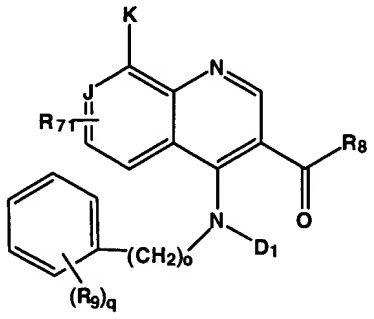
APPENDIX 1



II

wherein

R_8 is a lower alkyl group, an alkoxyalkyl group, an alkylaryl group, a cycloalkyl group, a cycloalkylalkyl group, an aryl group, an alkylaryl group, or K;

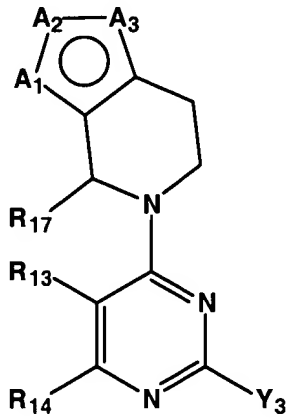
R_9 at each occurrence is independently a hydrogen, a lower alkyl group, an [akylthio] alkylthio group, a halogen, a cyano group an alkanoyl group, a haloalkyl group, a carbamoyl group, $-NR_7D_1$, $-OD_1$, or $-CO_2R_{12}$;

R_{71} is a hydrogen, a lower alkyl group, an alkoxy group, or $-OD_1$;

J, K, D_1, R_7, R_{12}, q and o are as defined herein; and

with the proviso that the compounds of Formula (II) must contain at least one nitrite, nitrate, thionitrite or thionitrate group.

Another embodiment of the present invention describes compounds of Formula (III) or pharmaceutically acceptable salts thereof:



III

wherein

nitrosylated through one or more sites such as oxygen, sulfur, carbon and/or nitrogen using the methods described in the examples herein and using conventional methods known to one skilled in the art. For example, known methods for nitrosating and nitrosylating compounds are described in U.S. Patent Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; and Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety. The methods of nitrosating and/or nitrosylating the compounds described in the examples herein and in these references can be applied by one skilled in the art to produce any of the nitrosated and/or nitrosylated proton pump inhibitors described herein.

Nitroso or nitro compounds of formula (**I**), where X is a –ONO, -SNO, or $-ONO_2$ group and R_1, R_2, R_3, R_4, R_5, R_{10}, R_{11}, A, B, J, R_e, R_f, and p are as defined herein, and a nitrite, nitrate, or thionitrite containing carbamate is representative of the D_1 group, as defined herein, may be prepared as shown in Scheme 1. The substituted imidazole nitrogen group of formula **1** is converted to the anion by treatment with one equivalent of a strong non-nucleophilic base, such as sodium hydride or [potasium] potassium hydride, in an aprotic solvent, such as tetrahydrofuran (THF) or dimethylformamide (DMF). The carbamate of formula **IA**, **IB**, or **IC** where p, X, R_e and R_f are as defined herein, is prepared by reacting the imidazole anion with a suitably functionalized chloroformate in an inert solvent, such as THF or DMF. Typically the coupling reaction is performed at a temperature ranging from –78 ^{0}C to room temperature. Preferred methods for the formation of chloroformates are reacting one equivalent of a X functionalized alcohol with one equivalent of phosgene at a temperature ranging from –78 ^{0}C to 0 ^{0}C in an inert solvent, such as ether or THF and in the presence of an amine base, such as pyridine or triethylamine. Removal of the amine hydrochloride by filtration affords a solution of the desired chloroformate which may be used directly or concentrated and redissolved in the anhydrous solution of choice prior to the coupling reaction with the imidazole anion to afford the carbamate of formula **IA**, **IB**, or **IC**.

On occasion it might be desirable to nitrosylate the alcohol or thiol after coupling a chloroformate to the imidazole anion. The chloroformate would be prepared by reacting phosgene with an alcohol containing a protected alcohol or

are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the nitrite, thionitrite, or nitrate containing acid. Preferred methods for preparing acid chlorides are treating the carboxylic acid with oxalyl chloride and a catalytic amount of DMF in an inert solvent, such as ether, THF, dichloromethane, or toluene. Preferred methods for preparing mixed anhydride are reacting the carboxylic acid with a chloroformate, such as isubutylchloroformate, in the presence of an amine base, such as triethylamine in an inert [solvent] solvent, such as ether, THF, dichloromethane, or toluene. Alternatively, the alcohol and nitrite, thionitrite, or nitrate containing acid may be condensed in the presence of a dehydrating agent, such as DCC or EDAC·HCl with or without a catalyst, such as DMAP or HOBt.

On occasion it might be desirable to nitrosylate the alcohol or thiol after coupling the activated acylating agent to the alcohol. The activated acylating agent would be prepared from an acid containing a protected alcohol or thiol moiety. Preferred protecting groups for an alcohol moiety are silyl ethers, such as a trimethylsilyl ether, a tert-butyldimethylsilyl ether, or a tert-butyldiphenylsilyl ether. After formation of the ester, deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as dichloromethane, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine affords the compound of formula **IIIA**. Preferred protecting groups for the thiol moiety are as a thioester, such as a thioacetate or a thiobenzoate or as a disulfide. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base or sodium methoxide in methanol is typically used to hydrolyze thioesters) followed by reaction with a suitable nitrosylating agent such, as thionyl chloride nitrite or thionyl dinitrite, a lower alkyl nitrite, such as tert-butyl nitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as methylene chloride, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine, affords the compound of formula **IIIB**. Nitrosation of the ester product may be accomplished by

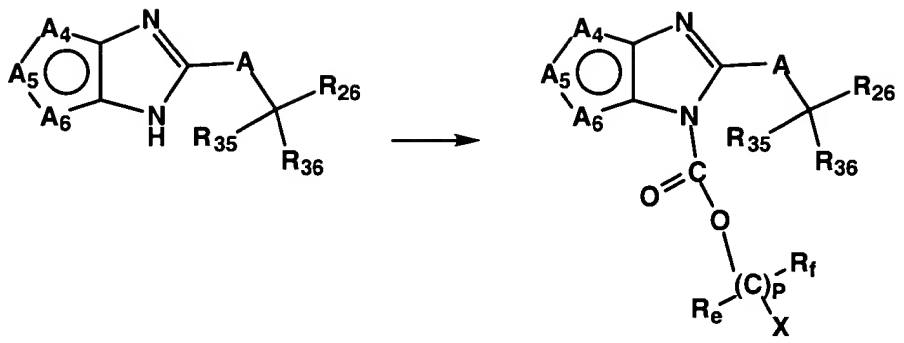
Preferred methods for preparing acid chlorides are treating the carboxylic acid with oxalyl chloride and a catalytic amount of DMF in an inert solvent, such as ether, THF, dichloromethane, or toluene. Preferred methods for preparing mixed anhydride are reacting the carboxylic acid with a chloroformate, such as isubutylchloroformate, in the presence of an amine base, such as triethylamine, in an inert [solvent] solvent, such as ether, THF, dichloromethane, or toluene. Alternatively, the alcohol and nitrite, thionitrite, or nitrate containing acid may be condensed in the presence of a dehydrating agent, such as DCC or EDAC·HCl, with or without a catalyst, such as DMAP or HOBt.

On occasion it might be desirable to nitrosylate the alcohol or thiol after coupling the activated acylating agent to the alcohol. The activated acylating agent would be prepared from an acid containing a protected alcohol or thiol moiety. Preferred protecting groups for an alcohol moiety are silyl ethers, such as a trimethylsilyl ether, a tert-butyldimethylsilyl ether, or a tert-butyldiphenylsilyl ether. After formation of the ester, deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as dichloromethane, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine affords the compound of formula **VA**. Preferred protecting groups for the thiol moiety are as a thioester, such as a thioacetate or a thiobenzoate or as a disulfide. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base or sodium methoxide in methanol is typically used to hydrolyze thioesters) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite, such as tert-butyl nitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as methylene chloride, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine, affords the compound of formula **VB**. Nitrosation of the ester product may be accomplished by first converting the deprotected alcohol to a leaving group, such as a mesylate or a tosylate. This reaction is typically performed at a temperature of 0 ^{0}C to room

-ONO_2 group and R_{26}, R_{35}, R_{36}, A, A_4, A_5, A_6, R_e, R_f, and p are as defined herein, and a nitrite, nitrate, or thionitrite containing carbamate is representative of the D_1 group, as defined herein, may be prepared as shown in Scheme 6. The substituted imidazole nitrogen group of formula **6** is converted to the anion by treatment with one equivalent of a strong non-nucleophilic base, such as sodium hydride or [potasium] potassium hydride in an aprotic solvent, such as THF or DMF. The carbamate of formula **VIA**, **VIB**, or **VIC** where p, X, R_e and R_f are as defined herein, is prepared by reacting the imidazole anion with a suitably functionalized chloroformate in an inert solvent, such as THF or DMF. Typically the coupling reaction is performed at a temperature ranging between –78 °C and room temperature. Preferred methods for the formation of cloroformates are reacting one equivalent of X functionalized alcohol with one equivalent of phosgene at a [tempeature] temperature ranging from –78 °C to 0 °C in an inert solvent, such as ether or THF, and in the presence of an amine base, such as pyridine or triethylamine. Removal of the amine hydrochloride by filtration affords a solution of the desired chloroformate which may be used directly or concentrated and redissolved in the anhydrous solution of choice prior to the coupling reaction with the imidazole anion to afford the carbamate of the formula **VIA**, **VIB**, or **VIC**.

On occasion it might be desirable to nitrosylate the alcohol or thiol after coupling a chloroformate to the imidazole anion. The chloroformate would be prepared by reacting phosgene with an alcohol containing a protected alcohol or thiol moiety. Preferred protecting groups for an alcohol moiety are silyl ethers, such as a trimethylsilyl ether, a tert-butyldimethylsilyl ether, or a tert-butyldiphenylsilyl ether. After formation of the carbamate, deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as dichloromethane, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine, affords the compound of formula **VIA**. Preferred protecting groups for the thiol moiety are as a thioester, such as a thioacetate or a thiobenzoate or as a disulfide. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are

Scheme 6



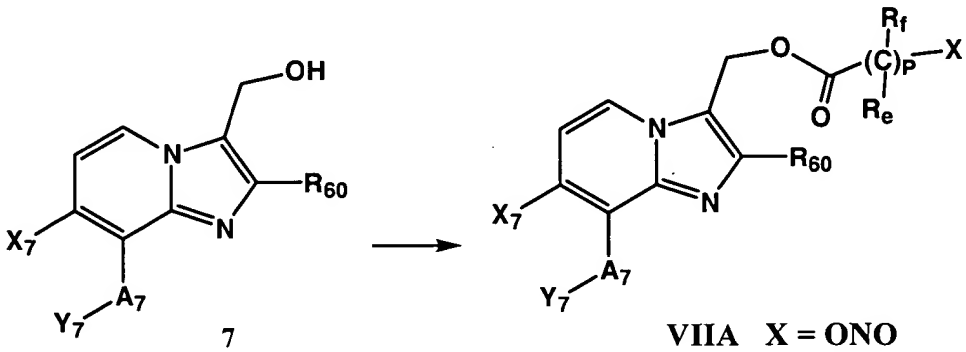
6

VIA X = ONO
VIB X = SNO
VIC X = ONO_2

Nitroso or nitro compounds of formula (**VII**), where X is a –ONO, -SNO, or -ONO_2 group and R_{60}, A_7, X_7, Y_7, R_e, R_f, and p, are as defined herein, and a nitrite, nitrate, or thionitrite containing acyl group is representative of the D group may be prepared as shown in Scheme 7. The hydroxyl group of formula **7** is converted to the ester of formula **VIIA**, **VIIB**, or **VIIC**, where p, R_e R_f and X are as defined herein, by reaction with an appropriate nitrite, thionitrite, or nitrate containing activated acylating agent. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the nitrite, thionitrite, or nitrate containing acid. Preferred methods for preparing acid chlorides are treating the carboxylic acid with oxalyl chloride and a catalytic amount of DMF in an inert solvent, such as ether, THF, dichloromethane, or toluene. Preferred methods for preparing mixed anhydride are reacting the carboxylic acid with a chloroformate, such as isubutylchloroformate, in the presence of an amine base, such as triethylamine, in an inert [solvent] solvent, such as ether, THF, dichloromethane, or toluene. Alternatively, the alcohol and nitrite, thionitrite, or

such as THF. Treatment of the bromide or iodide with silver nitrate in an inert solvent, such as acetonitrile, affords the compound of formula **VIIC**. Alternatively, the halide containing ester may be formed directly by preparing a halide containing active acylating agent from a halide containing acid. Preferred halides are bromide and iodide. Coupling of the alcohol with the halide containing active acylating agent followed by reaction of the ester product with silver nitrate in an inert solvent, such as acetonitrile, affords the compound of formula **VIIC**. Preferred coupling methods for the formation of esters from alcohols are those methods described herein (e.g. with the preformed acid chloride or anhydride or with the carboxylic acid and a dehydration agent, such as DCC or EDAC·HCl).

Scheme 7



VIIA X = ONO
VIIB X = SNO
VIIC X = ONO_2

The compounds of the present invention include proton pump inhibitors, such as those described herein, which have been nitrosated and/or nitrosylated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation), carbon and/or nitrogen. The nitrosated and/or nitrosylated proton pump inhibitors of the present invention are capable of donating, [transfering] transferring and/or releasing a biologically active form of nitrogen monoxide (i.e., nitric oxide).

Nitrogen monoxide can exist in three forms: NO- (nitroxyl), NO• (uncharged nitric oxide) and NO^+ (nitrosonium). NO• is a highly reactive short-lived species that is potentially toxic to cells. This is critical because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to the nitric

by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which can be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. The thiol precursor can also be nitrosylated by reaction with an organic nitrite such as tert-butyl nitrite, or a nitrosonium salt such as nitrosonium [tetraflurorborate] tetrafluoroborate in an inert solvent.

Another group of NO adducts for use in the present invention, where the NO adduct is a compound that donates, transfers or releases nitric oxide, include compounds comprising at least one ON-O-, ON-N- or ON-C- group. The compounds that include at least one ON-O-, ON-N- or ON-C- group are preferably ON-O-, ON-N- or ON-C-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O, ON-N- or ON-C-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON-O-, ON-N- or ON-C-sugars; ON-O-, ON-N- or ON-C- modified or unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); ON-O-, ON-N- or ON-C- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and ON-O-, ON-N- or ON-C-heterocyclic compounds.

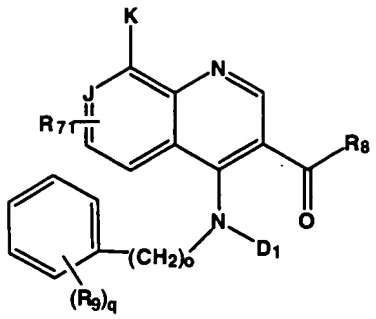
Another group of NO adducts for use in the present invention include nitrates that donate, transfer or release nitric oxide, such as compounds comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group. Preferred among these compounds are O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C-sugars; O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- modified and unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- heterocyclic compounds. Preferred examples of compounds comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group include isosorbide dinitrate,

or reverse gastrointestinal toxicity and/or to facilitate ulcer healing resulting from the NSAID and/or selective COX-2 inhibitor treatment. In yet another aspect of the present invention, the patient can be administered at least one NSAID and/or selective COX-2 inhibitor with a therapeutically effective amount of at least one proton pump inhibitor and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to decrease or reverse gastrointestinal toxicity and/or to facilitate ulcer healing resulting from the NSAID and/or selective COX-2 inhibitor treatment. The NSAID and/or selective COX-2 inhibitor, nitrosated and/or nitrosylated proton pump inhibitor, proton pump inhibitor, and/or nitric oxide donor can be administered separately or as components of the same composition. These compounds and/or compositions can also be provided in the form of a pharmaceutical kit.

The compounds and compositions of the present invention can be used in this aspect of the invention with any NSAID and selective COX-2 inhibitor known in the art. Such NSAIDs include, for example, aspirin (e.g., acetylsalicylic acid), salicylate esters and salts, acetate esters of salicylic acid, [diflurophenyl] difluorophenyl derivatives (e.g., diflunisal), salicylsalicylic acids (e.g., salsalate), salts of salicylic acids (e.g., sodium salicylate), salicylamide, sodium thiosalicylate, choline salicylate, magnesium salicylate, combinations of choline and magnesium salicylates, 5-aminosalicylic acid (e.g., mesalamine), salicylazosulfapyridine (e.g., sulfasalazine), methylsalicylate, and the like.

Another group of NSAIDs are the pyrazolon derivatives, which include, for example, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone and apazone (azapropazone). Another group of NSAIDs are the para-aminophenol derivatives, which are the so-called "coal tar" analgesics, including, for example, phenacetin and its active metabolite acetaminophen. Another group of compounds include indomethacin, a methylated indole derivative, and the structurally related compound sulindac. Yet another group of compounds is the fenamates which are derivatives of N-phenylanthranilic acid (e.g., mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamic acids). Another contemplated NSAID is tolmetin.

APPENDIX 2



II

wherein

R_8 is a lower alkyl group, an alkoxyalkyl group, an alkylaryl group, a cycloalkyl group, a cycloalkylalkyl group, an aryl group, an alkylaryl group, or K;

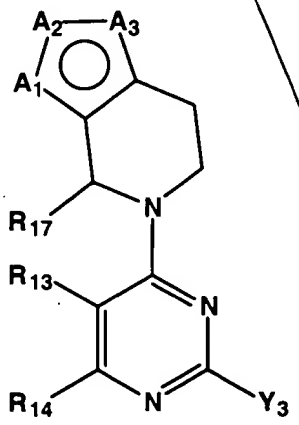
R_9 at each occurrence is independently a hydrogen, a lower alkyl group, an akylthio group, a halogen, a cyano group an alkanoyl group, a haloalkyl group, a carbamoyl group, $-NR_7D_1$, $-OD_1$, or $-CO_2R_{12}$;

R_{71} is a hydrogen, a lower alkyl group, an alkoxy group, or $-OD_1$;

J, K, D_1, R_7, R_{12}, q and o are as defined herein; and

with the proviso that the compounds of Formula (II) must contain at least one nitrite, nitrate, thionitrite or thionitrate group.

Another embodiment of the present invention describes compounds of Formula (III) or pharmaceutically acceptable salts thereof:



III

wherein

nitrosylated through one or more sites such as oxygen, sulfur, carbon and/or nitrogen using the methods described in the examples herein and using conventional methods known to one skilled in the art. For example, known methods for nitrosating and nitrosylating compounds are described in U.S. Patent Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; and Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety. The methods of nitrosating and/or nitrosylating the compounds described in the examples herein and in these references can be applied by one skilled in the art to produce any of the nitrosated and/or nitrosylated proton pump inhibitors described herein.

Nitroso or nitro compounds of formula (**I**), where X is a –ONO, -SNO, or $-ONO_2$ group and R_1, R_2, R_3, R_4, R_5, R_{10}, R_{11}, A, B, J, R_e, R_f, and p are as defined herein, and a nitrite, nitrate, or thionitrite containing carbamate is representative of the D_1 group, as defined herein, may be prepared as shown in Scheme 1. The substituted imidazole nitrogen group of formula **1** is converted to the anion by treatment with one equivalent of a strong non-nucleophilic base, such as sodium hydride or potasium hydride, in an aprotic solvent, such as tetrahydrofuran (THF) or dimethylformamide (DMF). The carbamate of formula **IA**, **IB**, or **IC** where p, X, R_e and R_f are as defined herein, is prepared by reacting the imidazole anion with a suitably functionalized chloroformate in an inert solvent, such as THF or DMF. Typically the coupling reaction is performed at a temperature ranging from –78 °C to room temperature. Preferred methods for the formation of chloroformates are reacting one equivalent of a X functionalized alcohol with one equivalent of phosgene at a temperature ranging from –78 °C to 0 °C in an inert solvent, such as ether or THF and in the presence of an amine base, such as pyridine or triethylamine. Removal of the amine hydrochloride by filtration affords a solution of the desired chloroformate which may be used directly or concentrated and redissolved in the anhydrous solution of choice prior to the coupling reaction with the imidazole anion to afford the carbamate of formula **IA**, **IB**, or **IC**.

On occasion it might be desirable to nitrosylate the alcohol or thiol after coupling a chloroformate to the imidazole anion. The chloroformate would be prepared by reacting phosgene with an alcohol containing a protected alcohol or

are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the nitrite, thionitrite, or nitrate containing acid. Preferred methods for preparing acid chlorides are treating the carboxylic acid with oxalyl chloride and a catalytic amount of DMF in an inert solvent, such as ether, THF, dichloromethane, or toluene. Preferred methods for preparing mixed anhydride are reacting the carboxylic acid with a chloroformate, such as isubutylchloroformate, in the presence of an amine base, such as triethylamine in an inert solvent solvent, such as ether, THF, dichloromethane, or toluene. Alternatively, the alcohol and nitrite, thionitrite, or nitrate containing acid may be condensed in the presence of a dehydrating agent, such as DCC or EDAC·HCl with or without a catalyst, such as DMAP or HOBt.

On occasion it might be desirable to nitrosylate the alcohol or thiol after coupling the activated acylating agent to the alcohol. The activated acylating agent would be prepared from an acid containing a protected alcohol or thiol moiety. Preferred protecting groups for an alcohol moiety are silyl ethers, such as a trimethylsilyl ether, a tert-butyldimethylsilyl ether, or a tert-butyldiphenylsilyl ether. After formation of the ester, deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as dichloromethane, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine affords the compound of formula **IIIA**. Preferred protecting groups for the thiol moiety are as a thioester, such as a thioacetate or a thiobenzoate or as a disulfide. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base or sodium methoxide in methanol is typically used to hydrolyze thioesters) followed by reaction with a suitable nitrosylating agent such, as thionyl chloride nitrite or thionyl dinitrite, a lower alkyl nitrite, such as tert-butyl nitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as methylene chloride, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine, affords the compound of formula **IIIB**. Nitrosation of the ester product may be accomplished by

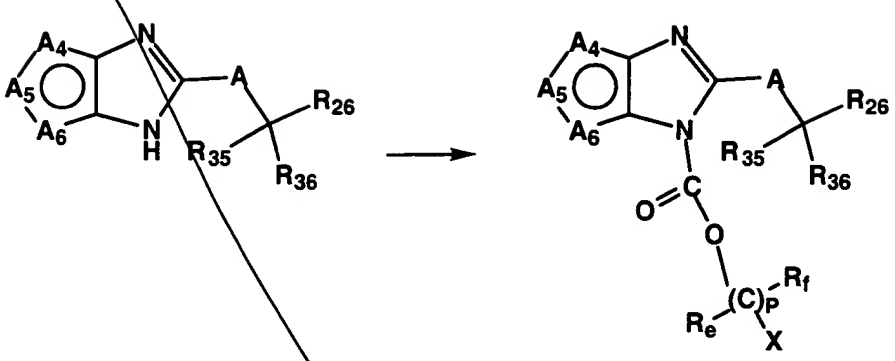
Preferred methods for preparing acid chlorides are treating the carboxylic acid with oxalyl chloride and a catalytic amount of DMF in an inert solvent, such as ether, THF, dichloromethane, or toluene. Preferred methods for preparing mixed anhydride are reacting the carboxylic acid with a chloroformate, such as isubutylchloroformate, in the presence of an amine base, such as triethylamine, in an inert solvent solvent, such as ether, THF, dichloromethane, or toluene. Alternatively, the alcohol and nitrite, thionitrite, or nitrate containing acid may be condensed in the presence of a dehydrating agent, such as DCC or EDAC·HCl, with or without a catalyst, such as DMAP or HOBt.

On occasion it might be desirable to nitrosylate the alcohol or thiol after coupling the activated acylating agent to the alcohol. The activated acylating agent would be prepared from an acid containing a protected alcohol or thiol moiety. Preferred protecting groups for an alcohol moiety are silyl ethers, such as a trimethylsilyl ether, a tert-butyldimethylsilyl ether, or a tert-butyldiphenylsilyl ether. After formation of the ester, deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as dichloromethane, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine affords the compound of formula **VA**. Preferred protecting groups for the thiol moiety are as a thioester, such as a thioacetate or a thiobenzoate or as a disulfide. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base or sodium methoxide in methanol is typically used to hydrolyze thioesters) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite, such as tert-butyl nitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as methylene chloride, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine, affords the compound of formula **VB**. Nitrosation of the ester product may be accomplished by first converting the deprotected alcohol to a leaving group, such as a mesylate or a tosylate. This reaction is typically performed at a temperature of 0 ^{0}C to room

-ONO_2 group and R_{26}, R_{35}, R_{36}, A, A_4, A_5, A_6, R_e, R_f, and p are as defined herein, and a nitrite, nitrate, or thionitrite containing carbamate is representative of the D_1 group, as defined herein, may be prepared as shown in Scheme 6. The substituted imidazole nitrogen group of formula **6** is converted to the anion by treatment with one equivalent of a strong non-nucleophilic base, such as sodium hydride or potasium hydride in an aprotic solvent, such as THF or DMF. The carbamate of formula **VIA**, **VIB**, or **VIC** where p, X, R_e and R_f are as defined herein, is prepared by reacting the imidazole anion with a suitably functionalized chloroformate in an inert solvent, such as THF or DMF. Typically the coupling reaction is performed at a temperature ranging between –78 °C and room temperature. Preferred methods for the formation of cloroformates are reacting one equivalent of X functionalized alcohol with one equivalent of phosgene at a tempeature ranging from –78 °C to 0 °C in an inert solvent, such as ether or THF, and in the presence of an amine base, such as pyridine or triethylamine. Removal of the amine hydrochloride by filtration affords a solution of the desired chloroformate which may be used directly or concentrated and redissolved in the anhydrous solution of choice prior to the coupling reaction with the imidazole anion to afford the carbamate of the formula **VIA**, **VIB**, or **VIC**.

On occasion it might be desirable to nitrosylate the alcohol or thiol after coupling a chloroformate to the imidazole anion. The chloroformate would be prepared by reacting phosgene with an alcohol containing a protected alcohol or thiol moiety. Preferred protecting groups for an alcohol moiety are silyl ethers, such as a trimethylsilyl ether, a tert-butyldimethylsilyl ether, or a tert-butyldiphenylsilyl ether. After formation of the carbamate, deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent, such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate, in a suitable anhydrous solvent, such as dichloromethane, THF, DMF, or acetonitrile, with or without an amine base, such as pyridine or triethylamine, affords the compound of formula **VIA**. Preferred protecting groups for the thiol moiety are as a thioester, such as a thioacetate or a thiobenzoate or as a disulfide. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are

Scheme 6



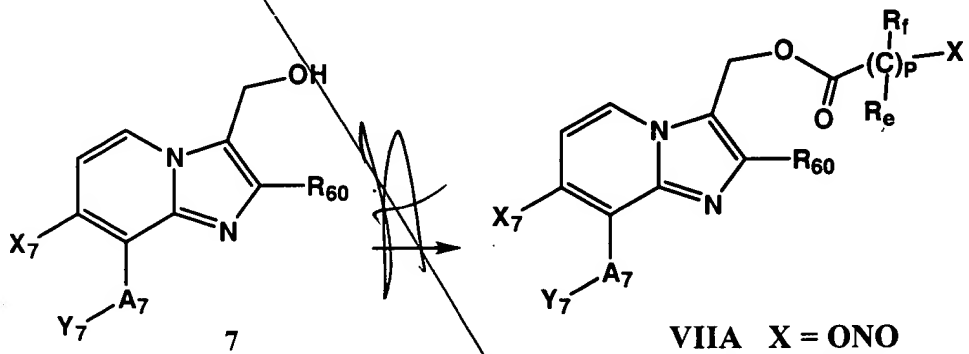
6

VIA X = ONO
VIB X = SNO
VIC X = ONO_2

Nitroso or nitro compounds of formula (**VII**), where X is a –ONO, -SNO, or -ONO_2 group and R_{60}, A_7, X_7, Y_7, R_e, R_f, and p, are as defined herein, and a nitrite, nitrate, or thionitrite containing acyl group is representative of the D group may be prepared as shown in Scheme 7. The hydroxyl group of formula **7** is converted to the ester of formula **VIIA**, **VIIB**, or **VIIC**, where p, R_e R_f and X are as defined herein, by reaction with an appropriate nitrite, thionitrite, or nitrate containing activated acylating agent. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the nitrite, thionitrite, or nitrate containing acid. Preferred methods for preparing acid chlorides are treating the carboxylic acid with oxalyl chloride and a catalytic amount of DMF in an inert solvent, such as ether, THF, dichloromethane, or toluene. Preferred methods for preparing mixed anhydride are reacting the carboxylic acid with a chloroformate, such as isubutylchloroformate, in the presence of an amine base, such as triethylamine, in an inert solvent solvent, such as ether, THF, dichloromethane, or toluene. Alternatively, the alcohol and nitrite, thionitrite, or

such as THF. Treatment of the bromide or iodide with silver nitrate in an inert solvent, such as acetonitrile, affords the compound of formula **VIIC**. Alternatively, the halide containing ester may be formed directly by preparing a halide containing active acylating agent from a halide containing acid. Preferred halides are bromide and iodide. Coupling of the alcohol with the halide containing active acylating agent followed by reaction of the ester product with silver nitrate in an inert solvent, such as acetonitrile, affords the compound of formula **VIIC**. Preferred coupling methods for the formation of esters from alcohols are those methods described herein (e.g. with the preformed acid chloride or anhydride or with the carboxylic acid and a dehydration agent, such as DCC or EDAC·HCl).

Scheme 7



VIIA X = ONO
VIIB X = SNO
VIIC X = ONO_2

The compounds of the present invention include proton pump inhibitors, such as those described herein, which have been nitrosated and/or nitrosylated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation), carbon and/or nitrogen. The nitrosated and/or nitrosylated proton pump inhibitors of the present invention are capable of donating, transfering and/or releasing a biologically active form of nitrogen monoxide (i.e., nitric oxide).

Nitrogen monoxide can exist in three forms: NO- (nitroxyl), NO• (uncharged nitric oxide) and NO^+ (nitrosonium). NO• is a highly reactive short-lived species that is potentially toxic to cells. This is critical because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to the nitric

by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which can be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. The thiol precursor can also be nitrosylated by reaction with an organic nitrite such as tert-butyl nitrite, or a nitrosonium salt such as nitrosonium tetraflurorborate in an inert solvent.

Another group of NO adducts for use in the present invention, where the NO adduct is a compound that donates, transfers or releases nitric oxide, include compounds comprising at least one ON-O-, ON-N- or ON-C- group. The compounds that include at least one ON-O-, ON-N- or ON-C- group are preferably ON-O-, ON-N- or ON-C-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O, ON-N- or ON-C-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON-O-, ON-N- or ON-C-sugars; ON-O-, ON-N- or ON-C- modified or unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); ON-O-, ON-N- or ON-C- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and ON-O-, ON-N- or ON-C-heterocyclic compounds.

Another group of NO adducts for use in the present invention include nitrates that donate, transfer or release nitric oxide, such as compounds comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group. Preferred among these compounds are O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C-sugars; O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- modified and unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- heterocyclic compounds. Preferred examples of compounds comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group include isosorbide dinitrate,

or reverse gastrointestinal toxicity and/or to facilitate ulcer healing resulting from the NSAID and/or selective COX-2 inhibitor treatment. In yet another aspect of the present invention, the patient can be administered at least one NSAID and/or selective COX-2 inhibitor with a therapeutically effective amount of at least one proton pump inhibitor and at least one compound that donates, transfers or releases nitric oxide, or elevates endogenous levels of nitric oxide or EDRF, or is a substrate for nitric oxide synthase, to decrease or reverse gastrointestinal toxicity and/or to facilitate ulcer healing resulting from the NSAID and/or selective COX-2 inhibitor treatment. The NSAID and/or selective COX-2 inhibitor, nitrosated and/or nitrosylated proton pump inhibitor, proton pump inhibitor, and/or nitric oxide donor can be administered separately or as components of the same composition. These compounds and/or compositions can also be provided in the form of a pharmaceutical kit.

The compounds and compositions of the present invention can be used in this aspect of the invention with any NSAID and selective COX-2 inhibitor known in the art. Such NSAIDs include, for example, aspirin (e.g., acetylsalicylic acid), salicylate esters and salts, acetate esters of salicylic acid, diflurophenyl derivatives (e.g., diflunisal), salicylsalicylic acids (e.g., salsalate), salts of salicylic acids (e.g., sodium salicylate), salicylamide, sodium thiosalicylate, choline salicylate, magnesium salicylate, combinations of choline and magnesium salicylates, 5-aminosalicylic acid (e.g., mesalamine), salicylazosulfapyridine (e.g., sulfasalazine), methylsalicylate, and the like.

Another group of NSAIDs are the pyrazolon derivatives, which include, for example, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone and apazone (azapropazone). Another group of NSAIDs are the para-aminophenol derivatives, which are the so-called "coal tar" analgesics, including, for example, phenacetin and its active metabolite acetaminophen. Another group of compounds include indomethacin, a methylated indole derivative, and the structurally related compound sulindac. Yet another group of compounds is the fenamates which are derivatives of N-phenylanthranilic acid (e.g., mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamic acids). Another contemplated NSAID is tolmetin.

APPENDIX 3

Appendix 3 – Pending Claims

What is claimed is:

35. (Amended) A composition comprising at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

36. The composition of claim 35, wherein the at least one proton pump inhibitor compound is a benzimidazole, a quinoline, a pyrimidine, a thiadiazole, a sulfinylnicotinamide, a thienoimidazole, or a imidazopyridine.

37. (Amended) The compound of claim 36, wherein the benzimidazole is omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, a tricyclic imidazole, a thienopydidine benzimidazole, a fluoroalkoxy substituted benzimidazole, a dialkoxy benzimidazole, a N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, a cycloheptenepyridine, a 5-pyrrolyl-2-pyridylmethylsulfinyl benzimidazole, a alkylsulfinyl benzimidazole, a fluoro-pyridylmethylsulfinyl benzimidazole, an imidazo(4,5-b)pyridine, RO 18-5362 or IY 81149; wherein the quinoline is a 4-amino-3-carbonyl quinoline, a 4-amino-3-acylnaphthyride, a 4-aminoquinoline, a 4-amino-3-acylquinoline or a 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline; wherein the pyrimidine is a quinazoline, a tetrahydroisoquinolin-2-yl pyrimidine or YH 1885; wherein the thiadiazole is 3-substituted 1,2,4-thiadiazolo(4,5-a) benzimidazole or a 3-substituted imidazo(1,2-d)-thiadiazole; wherein the sulfinylnicotinamide is a 2-sulfinylnicotinamide; wherein the thienoimidazole is a pyridylsulfinylbenz imidazole, a pyridylsulfinyl thieno imidazole, a theinoimidazole-toluidine, a 4,5-dihydrooxazole, a thienoimidazole-toluidine or Hoe-731; wherein the imidazopyridine is a imidazo(1,2-a)pyridine, a pyrrolo(2,3-b)pyridine or a pharmaceutically acceptable salt thereof.

38. The composition of claim 37 further comprising a pharmaceutically acceptable carrier.

39. (Amended) The composition of claim 35, wherein the compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or

A7 Cont

endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is an S-nitrosothiol.

40. The composition of claim 39, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

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41. The composition of claim 39, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; and

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q , or $(C(R_e)(R_f))_k$-T-Q, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, $-CH_2\text{-}C(T\text{-}Q)(R_e)(R_f)$, or $-(N_2O_2\text{-})^-\bullet M^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-CH_2\text{-}C(T\text{-}Q)(R_e)(R_f)$ or $-(N_2O_2\text{-})\bullet M^+$; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

42. (Amended) The composition of claim 35, wherein the compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids or inhibitors of the enzyme arginase.

43. (Amended) The composition of claim 35, wherein the compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N-, O_2N-S- or -O_2N-C- group;

(iii) a N-oxo-N-nitrosoamine having the formula: R^1R^2-N(O-M^+)-NO, wherein R^1 and R^2 are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

44. The composition of claim 43, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypepetide, an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

45. The composition of claim 43, wherein compound comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-C-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino

acid, an O_2N-C-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-C-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-oligonucleotide, an O_2N-C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-C-hydrocarbon, an O_2N-O-heterocyclic compound, an O_2N-N-heterocyclic compound, an O_2N-S-heterocyclic compound or an O_2N-C-heterocyclic compound.

46. The composition of claim 35, further comprising at least one of a nonsteroidal antiinflammatory drug, a selective COX-2 inhibitor, an antacid, a bismuth-containing reagent and an acid-degradable antibacterial compound.

47. A method for treating or preventing a gastrointestinal disorder, facilitating ulcer healing, or decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 35.

48. The method of claim 47, further comprising administering to the patient a therapeutically effective amount of an antacid.

49. The method of claim 47, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

50. A method for improving the gastroprotective properties, the anti- *Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor comprising administering to a patient in need thereof a therapeutically effective amount of the composition of claim 35.

51. The method of claim 50, further comprising administering to the patient a therapeutically effective amount of a bismuth-containing reagent.

52. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective

COX-2 inhibitor to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one composition of claim 35, and, optionally, at least one nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor.

53. A method for treating *Helicobacter pylori* comprising administering to a patient in need thereof a therapeutically effective amount of at least one acid degradable antibacterial compound and at least one composition of claim 35.

54. A method for treating a viral infection comprising administering to a patient in need thereof a therapeutically effective amount of the composition of claim 35.

55. The method of claim 54, wherein the viral infection is orthomyxoviridae, paramyxoviridae, picornaviridae, rhabdoviridae, coronavaridae, togaviridae, bunyaviridae, arenaviridae, reteroviridae, adenoviridae, proxviridae, papovaviridae, herpetoviridae, herpesviridae, herpes simplex viruses, cytomegalovirus, herpes varicella-zoster, Epstein-Barr, HHV6, HHV7, pseudorabies or rhinotracheitis.

59. (Amended) A method for preventing or treating a gastrointestinal disorder, facilitating ulcer healing, or decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

60. The method of claim 59, further comprising administering at least one antacid.

61. The method of claim 59, wherein the gastrointestinal disorder wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

64. A method for improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of a proton pump inhibitor compound comprising

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administering to a patient in need thereof a therapeutically effective amount of a bismuth complex comprising at least one composition of claim 35.

66. (Amended) A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, and, optionally, at least one nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor.

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68. (Amended) A method for treating *Helicobacter pylori* comprising administering to a patient in need thereof a therapeutically effective amount of at least one acid degradable antibacterial compound, at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

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71. (Amended) A method for treating a viral infection comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

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72. The method of claim 71, wherein the viral infection is orthomyxoviridae, paramyxoviridae, picornaviridae, rhabdoviridae, coronavaridae, togaviridae, bunyaviridae, arenaviridae, reteroviridae, adenoviridae, proxviridae, papovaviridae, herpetoviridae, herpesviridae, herpes simplex viruses, cytomegalovirus, herpes varicella-zoster, Epstein-Barr, HHV6, HHV7, pseudorabies or rhinotracheitis.

76. (Amended) A kit comprising at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived

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relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase

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77. (Amended) The kit of claim 76, wherein the proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and the compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase are separate components in the kit or are in the form of a composition in the kit.

78. The kit of claim 76, further comprising at least one of a nonsteroidal antiinflammatory drug, a selective COX-2 inhibitor, an antacid, a bismuth-containing reagent and an acid-degradable antibacterial compound.

APPENDIX 4

Appendix 4

AMENDMENTS TO CLAIMS – July 2001

Cancel claims 1-34 without prejudice

35. (Amended) A composition comprising at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, [or] induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

37. (Amended) The compound of claim 36, wherein the benzimidazole is omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, a tricyclic imidazole, a thienopydidine benzimidazole, a fluoroalkoxy substituted benzimidazole, a dialkoxy benzimidazole, a N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, a cycloheptenepyridine, a 5-pyrrolyl-2-pyridylmethylsulfinyl benzimidazole, a alkylsulfinyl benzimidazole, a fluoro-pyridylmethylsulfinyl benzimidazole, an imidazo~~[4,5-b]~~ (4,5-b)pyridine, RO 18-5362 or IY 81149; wherein the quinoline is a 4-amino-3-carbonyl quinoline, a 4-amino-3-acylnaphthyride, a 4-aminoquinoline, a 4-amino-3-acylquinoline or a 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline; wherein the pyrimidine is a quinazoline, a tetrahydroisoquinolin-2-yl pyrimidine or YH 1885; wherein the thiadiazole is 3-substituted 1,2,4-thiadiazolo~~[4,5-a]~~ (4,5-a) benzimidazole or a 3-substituted imidazo~~[1,2-d]~~ (1,2-d)-thiadiazole; wherein the sulfinylnicotinamide is a 2-sulfinylnicotinamide; wherein the thienoimidazole is a pyridylsulfinylbenz imidazole, a pyridylsulfinyl thieno imidazole, a theinoimidazole-toluidine, a 4,5-dihydrooxazole, a thienoimidazole-toluidine or Hoe-731; wherein the imidazopyridine is a imidazo~~[1,2-a]~~ (1,2-a)pyridine, a pyrrolo~~[2,3-b]~~ (2,3-b)pyridine or a pharmaceutically acceptable salt thereof.

39. (Amended) The composition of claim 35, wherein the compound that donates, transfers or releases nitric oxide, [or] induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is an S-nitrosothiol.

42. (Amended) The composition of claim 35, wherein the compound that donates, transfers or releases nitric oxide, [or] induces the production of endogenous nitric oxide or

endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids or inhibitors of the enzyme arginase.

43. (Amended) The composition of claim 35, wherein the compound that donates, transfers or releases nitric oxide, [or] induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N-, O_2N-S- or -O_2N-C- group;

(iii) a N-oxo-N-nitrosoamine having the formula: R^1R^2-N(O-M^+)-NO, wherein R^1 and R^2 are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

Cancel claims 56-58, without prejudice.

59. (Amended) A method for preventing or treating a gastrointestinal disorder, facilitating ulcer healing, or decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, [or] induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Cancel claims 62 and 63, without prejudice.

Cancel claim 65, without prejudice.

66. (Amended) A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound, and at least one compound that donates, transfers or releases nitric oxide, [or] induces the production

of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, and, optionally, at least one nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor.

Cancel claim 67, without prejudice.

68. (Amended) A method for treating *Helicobacter pylori* comprising administering to a patient in need thereof a therapeutically effective amount of at least one acid degradable antibacterial compound, at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, [or] induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Cancel claim 69 and 70, without prejudice.

71. (Amended) A method for treating a viral infection comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, [or] induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Cancel claims 73-75, without prejudice.

76. (Amended) A kit comprising at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, [or] induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase

77. (Amended) The kit of claim 76, wherein the proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and the compound that donates, transfers or releases nitric oxide, [or] induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase are separate components in the kit or are in the form of a composition in the kit.